Summer 2023

Discover

News from Brain Research Foundation

In This Issue

Dear Friends,

As the nation's oldest brain research organization, we exist to accelerate discoveries of the human brain. This year Brain Research Foundation is celebrating 70 years of supporting innovative neuroscience research.

Seven decades may seem like a long time pursuing our mission for novel treatments and cures of neurological diseases, but the brain is our most complex body part. The human brain is comprised of approximately 100 billion neurons that on their own can't do much, but when they connect and create networks, they control breathing, movement, and memories. This complexity is wonderful when we think about how it makes us each unique…but there is so much of it that we don't understand. That is where we come in.

Each research grant that we fund provides scientists with "start-up money" to fund their boldest ideas and start them moving in a direction that will lead them to breakthroughs. Some breakthroughs may be small, while some are major— all are impactful.

Our unique approach of funding a broad scope of projects enables scientists to explore a wide range of neurological questions. In this issue, we feature examples of research projects we're funding that are making a difference in many areas of neuroscience, studying the mechanisms behind the regulation of thirst, brain development, and the causes of autoimmune disorders of the nervous system.

Without BRF's initial investment, many projects, like those above, may have been hindered or perhaps never been funded at all. Your generous support enables us to fund the most high-impact and promising brain research.

I hope this newsletter inspires you to continue to partner with us to hasten new treatments and cures for neurological disorders. Thank you for your support.

Sincerely,

Terre A. Constantine, Ph.D.
Executive Director and CEO

70 YEARS OF ACCOMPLISHMENTS

1953
Brain Research Foundation established and incorporated as a not-for-profit organization

1958
Brain Research Foundation sponsors its first scientific conference

1963
Women's Council of the Brain Research Foundation is formed

1964
Brain Research Foundation partners with the University of Chicago to establish the Brain Research Institute

1981
Brain Research Foundation Seed Grant Program is created

1993
Brain Research Foundation raises $3 million to fund construction of Center for Molecular Neurobiology at the University of Chicago

1999
Brain Research Foundation holds first Neuroscience Day for Chicago area neuroscientists

2002
First Women's Council Brain Research Foundation Seed Grant is awarded

Our New SRC Member

Brain Research Foundation's Scientific Review Committee (SRC) is made up of well-regarded researchers in the field of neuroscience. This committee lends its scientific expertise when reviewing the various research proposals submitted to the Foundation, evaluating proposals and making suggestions for funding.

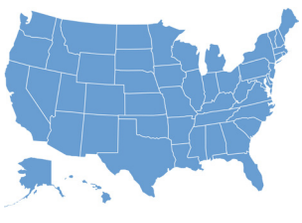
We're pleased to introduce our newest member, Dr. Craig Blackstone.

Craig Blackstone, M.D., Ph.D., is Chief of the Movement Disorders Division at the Massachusetts General Hospital and Professor of Neurology at Harvard Medical School. Previously, he was a Senior Investigator in the Intramural Research Program of the National Institute of Neurological Disorders and Stroke for nearly two decades.

Dr. Blackstone's research group investigates the cellular and molecular mechanisms underlying hereditary neurological movement disorders.

He is an elected member of the American Society for Clinical Investigation and Association of American Physicians, as well as an elected Fellow and former Vice President of the American Neurological Association (ANA). He has held numerous other leadership positions in the ANA, including on its Executive Council, Education Innovation Committee, Nominations Committee, Professional Development Committee, Translational and Clinical Research Course Committee, Web Governance Committee, and Research Careers Reimagined Subcommittee.

He serves on the editorial board of the Journal of Clinical Investigation. He received the NIH Director's Ruth L. Kirschstein Mentoring Award in 2012 and the NINDS Director's Diversity Achievement Award in 2018. In 2022, he was elected to the National Academy of Medicine.



2009
Brain Research Foundation expands its geographic grantmaking reach to all of Illinois; Children's Brain Research Foundation merges with Brain Research Foundation

2011
The Scientific Innovations Award Program is created to fund senior investigators; Partnered to educate Chicago Public Schools about concussion safety

2012
Special Research Initiative: Youth Sports Concussion Evaluation Grant

2013
Brain Research Foundation expands its geographic grantmaking reach nationwide

2014
Special Research Initiative: Exercise and Cognitive Decline Grant

2018
Special Research Initiative: Opioid Relapse Reduction Grant

2023
Brain Research Foundation celebrates 70 years of supporting the nation's most innovative brain research

BRF Funding Supports Scien How Research is Done

A sex bias-busting discovery[1] by two BRF grantees is poised to boost the use of female mice in research, demonstrating our approach to funding the most innovative, risk-taking scientists powers field-changing advances.

A new study co-authored by 2016 BRF Seed Grant Award winner Rebecca Shansky, Ph.D., associate professor in the Department of Psychology at Northeastern University in Boston, and 2020 BRF Scientific Innovations Award winner Sandeep Robert Datta, M.D., Ph.D., professor In the Department of Neurobiology at Harvard Medical School in Boston shatters the myth of reproductive cycle-linked behavioral variability in female mice (a 2018 analysis showed that only 1 in 5 brain studies included male and female mice[2]). Instead, their study shows female exploratory behavior is more stable than male mouse behavior and doesn't vary with reproductive cycles.

By identifying the boldest ideas by the most innovative researchers, BRF's funding supports the groundwork for scientific breakthroughs.

Moving the Needle

Leveraging Dr. Shansky's expertise in studying sex differences and Dr. Datta's cutting-edge behavioral analysis tool allowed them to not only debunk a longstanding sex bias in science, but to also revealed tremendous individuality in mouse behavioral patterns.

Their BRF-supported discoveries add to the data backing a 2016 policy requiring NIH grant-funded researchers to use both sexes in research unless they can demonstrate a sound reason not to.[3] Already more labs are using female mice, Dr. Shansky said, resulting in provocative discoveries about sex differences and brain function more generally.

"The needle is definitely moving, and our paper is another little push," she said. The study has garnered a lot of attention, including a feature in the New York Times.[4]

Terre A. Constantine, Ph.D., BRF Executive Director and CEO, added "BRF-funded studies challenge longstanding sex bias in scientific research, demonstrating that BRF is not only advancing scientific knowledge, but we are changing the boundaries of how science is done."

This sex imbalance reduces the applicability of studies' results. For example, Dr. Datta noted that most drugs used to treat brain disorders were tested in animal studies using only males.

The study reinforces the need for scientists to check their pre-existing biases and run experiments with animals from both sexes or to choose the sex most appropriate for their study, said Dr. Datta. He noted well-documented sex differences in neurodevelopmental diseases like autism and neurodegenerative ones like Alzheimer's that require consideration of sex differences. It also demonstrates the power of BRFs approach to funding scientists with the vision and courage to challenge long-held assumptions in their fields.

"It's clear that both drugs and diseases differentially affect males and females," Dr. Datta said. "If our goal is in an equitable way to address the challenges associated with psychiatric or neurological disorders, then it is critical to consider sex a variable in our experiments."

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1. Levy DR, Hunter N, Lin S, Robinson EM, Gillis W, Conlin EB, Anyoha R, Shansky RM, Datta SR. Mouse spontaneous behavior reflects individual variation rather than estrous state. Curr Biol. 2023 Apr 10;33(7):1358-1364. e4. doi: 10.1016/j.cub.2023.02.035. Epub 2023 Mar 7. PMID: 36889318; PMCID: PMC10090034.

2. National Institutes of Health. NIH Policy on Sex as a Biological Variable. https://orwh.od.nih.gov/sex-gender/nih-policy-sex-biological-variable. Accessed April 18, 2023.

3. Beery AK. Inclusion of females does not increase variability in rodent research studies. Curr Opin Behav Sci. 2018 Oct;23:143-149. doi: 10.1016/j.cobeha.2018.06.016. Epub 2018 Aug 2. PMID: 30560152; PMCID: PMC6294461.

4. Azeen Ghorayshi. Guess Which Sex Behaves More Erratically (at Least in Mice). New York Times. March 7, 2023. https://www.nytimes.com/2023/03/07/science/female-mice-hormones.html. Accessed April 18, 2023.

tists Challenging

Pivotal BRF Support

The $80,000 2016 Seed Grant from BRF came at a pivotal moment for Dr. Shansky. Her laboratory desperately needed an infusion of funding to continue dissecting sex-specific mechanisms of fear and emotion processing in rats. The work lays the basic science foundation for understanding why some brain conditions, like post-traumatic stress disorder, affect women more frequently.

"Getting the BRF grant when we did was game-changing," she said. "Everything we've been studying since receiving the grant has been about understanding the way males and females are different and how they express fear and the underlying brain circuits."

The BRF Seed Grant allowed Dr. Shansky to purchase software and build a customized tool that automates the analysis of rat behaviors. The BRF funding enabled Dr. Shansky and her colleagues to discover a female-specific fear behavior called darting. Since then, the team has been working to understand why the animals dart and identify the underlying brain circuits in the prefrontal cortex.

"Activation of this circuit in female rats puts them in a frame of mind where they do better on tasks that involve cognitive flexibility, including the extinction of the fear response," she said.

In addition to enabling this field-changing discovery, the BRF grant and the resulting data allowed Dr. Shansky to secure four more grants totaling $2.2 million from the National Institute of Mental Health to continue and expand her laboratory's work. Now, she and her team are studying the effects of inhibiting the circuit.

Her BRF-funded darting discovery is also changing the way other brain scientists conduct studies. "Darting behavior is now widely recognized through my field as a key metric, and I genuinely believe that we have changed the way behavioral neuroscientists think about a longstanding and widely used paradigm," Dr. Shansky said. "We have revealed systemic biases within the field and broadened ideas about how to measure fear."

Dr. Datta's $150,000 two-year 2020 BRF Scientific Innovations grant was crucial in helping him build the automated machine learning-driven motion sequencing platform used in the study he co-authored with Dr. Shansky. The tool breaks down behavior into small actions or "syllables" to allow the team to analyze behaviors more granularly and hopefully yield insights on brain diseases like Alzheimer's or autism that affect behavior.

Rebecca Shansky, Ph.D.

Sandeep Robert Datta, M.D., Ph.D.

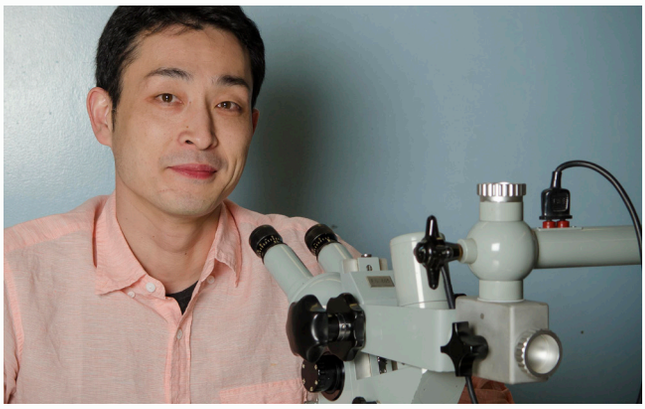
Previously, Dr. Datta noted, researchers relied on manually analyzing behavioral snapshots and averaging them, which blurred out individual differences in animal behavior.

Dr. Datta said that traditional funding sources disincentivize the development of such new technologies, which may hold the field of neuroscience back. But by funding the boldest ideas by the bravest researchers, the BRF's Scientific Innovations Awards lay the groundwork for field-changing breakthroughs.

"The funding provided by BRF has facilitated my ability to take risks and be creative in the choices we made to build the best tools possible to understand the brain," he explained.

Selected by our Scientific Review Committee and Board of Trustees, BRF's Scientific Innovations Award Winners and Seed Grant Winners advance neuroscience and the understanding of neurological diseases.

2023 Scientific Innovations Award Grantees



Yuki Oka, Ph.D., California Institute of Technology
Project Title: Molecular Mechanisms of Osmolality Sensing in the Mammalian Brain

Keywords: Osmosensor, homeostasis, brain thirst circuit

Animals constantly detect and process sensory signals to react appropriately. External sensory information (e.g., light and sound) serves as prominent environmental clues to guide behavior. On the other hand, our body monitors internal parameters like temperature, pressure, and osmolality. Osmolality sensing plays an essential role in homeostatic regulation, such as blood pressure, renal function, and thirst perception. Nevertheless, little is known about how the brain and body sense osmolality. Dr. Oka's study investigates this important biological question using the brain thirst circuit. **Molecular identification of osmosensors will be a springboard for understanding human diseases related to malfunction of this regulation leads to severe symptoms and diseases, including hypertension and renal dysfunction.**

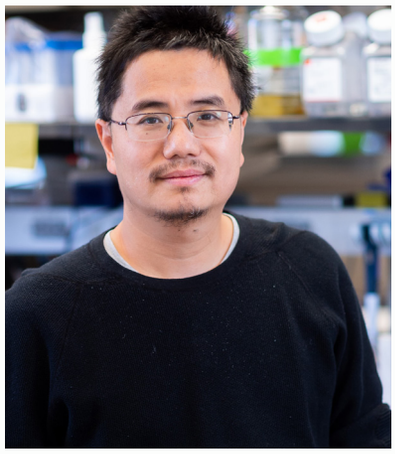
Jason Shepherd, Ph.D., University of Utah
Project Title: Virus-like Intercellular Signaling Underlying Autoimmune Neurological Disorders

Keywords: Intercellular signaling, autoimmune disorders, cancer, viruses

Dr. Shepherd's lab discovered that a brain gene critical for memory and cognition, Arc, has biochemical properties like retroviruses such as HIV. Arc can form virus-like protein capsids (capsules or shells) that shuttle RNA and proteins cell-to-cell. The lab found another family of genes that are expressed in the brain can form capsids.

These paraneoplastic Ma antigen (PNMA) genes sometimes cause neurological disorders when abnormally expressed in certain kinds of cancers due to an autoimmune response. It is unclear how these particular genes activate the immune system to generate self-antibodies. They hypothesize that abnormal expression of PNMA virus-like capsids outside the brain are the cause of auto-antibody production and the resulting neurological symptoms. **This project will uncover new signaling pathways in the brain and reveal the causes of some autoimmune neurological disorders.**

Chaolin Zhang, Ph.D., Columbia University
Project Title: Human-specific Alternative Splicing, Brain Development, and Ciliopathies



Keywords: Brain development, evolution, human-specific alternative splicing

Like movie frames needing to be edited to tell an engaging story, pieces of genetic information in DNA for each gene need to be sliced and rejoined, through a process called "splicing" to produce the RNA "transcripts" that dictate protein translation. RNA splicing patterns can diverge across different species during evolution and human-specific splicing patterns may contribute to why human is human. Not only does this include our unparalleled cognitive capacities and problem-solving skills, but also why humans are susceptible to diseases, including certain neural developmental disorders and dementia. Dr. Zhuang recently found human-specific splicing patterns frequently occur in a group of genes related to a cell organelle named cilium. Cilia are tiny hair-like structures that protrude from the surface of nearly all mammalian cells to sense their environments and participate in cell-cell communications, which is critical for the development of human organs, including the brain. **Dr. Zhuang aims to understand the function of these human-specific splicing events, how they might contribute to brain development, and how mutations disrupting such events might be linked to ciliopathies, such as Joubert and Merckel syndromes currently with tremendous unmet medical needs.**

2023 Seed Grant Winners

Rebekah C. Evans, Ph.D.
Georgetown University
Department of Neuroscience

Project Title: In Vivo and Ex Vivo Dissection of Midbrain Neuron Activity During Exercise

Keywords: Exercise, brain health, Alzheimer's disease, Parkinson's disease, neurodegenerative disorders

DEMENTIA SOCIETY OF AMERICA SEED GRANT

William J. Giardino, Ph.D.
Stanford University
Department of Psychiatry and Behavioral Sciences

Project Title: Deciphering the Neuropeptide Circuitry of Emotional Arousal in Narcolepsy

Keywords: Narcolepsy, sleep disorders, mental health conditions

Howard Gritton, Ph.D.
University of Illinois
Department of Comparative Biosciences

Project Title: Attention Mechanisms Contributing to Auditory Spatial Processing

Keywords: Sound processing; autism spectrum disorder (ASD); attention deficit/hyperactivity disorder (ADD/ADHD)

Nora Kory, Ph.D.
Harvard University
Department of Molecular Metabolism

Project Title: Elucidating the Fates and Functions of Lactate in the Brain

Keywords: Epilepsy, neurodegenerative and psychiatric disorders, brain metabolism

Hojoon Lee, Ph.D.
Northwestern University
Department of Neurobiology

Project Title: Deciphering the Neural Circuitry of Nausea

Keywords: Nausea, motion sickness, brain stem

Huaijin Ken Leon Loh, Ph.D.
Yale University
Department of Comparative Medicine

Project Title: Synapses in the Periphery: Uncovering Molecular Connections Between Nerves and Organs

Keywords: Autonomic nervous system, synapses, peripheral neuropathies, diabetes

Eirene Markenscoff-Papadimitriou, Ph.D.
Cornell University
Department of Molecular Biology and Genetics

Project Title: Neuronal Vulnerability to Heterochromatin Dysregulation in Development

Keywords: Autism spectrum disorder, neurodevelopment disorders, cellular diversity

CARL & MARILYNN THOMA FOUNDATION SEED GRANT

Bridget Ostrem, M.D., Ph.D.
University of California San Francisco
Department of Neurology

Project Title: Investigating the Therapeutic Potential of Human Milk Oligosaccharides

Keywords: Cerebral palsy, white matter injury, preterm birth

WOMEN'S COUNCIL SEED GRANT

Benjamin Scholl, Ph.D.
University of Pennsylvania
Department of Neuroscience

Project Title: Elucidating Synapse Dysfunction Using In Vivo Single-Cell CRISPR/Cas9 Manipulations

Keywords: Autism spectrum disorder, Fragile X Syndrome,synapse dysfunction

Natale R. Sciolino, Ph.D.
University of Connecticut
Department of Physiology and Neurobiology

Project Title: Impact of Locus Coeruleus Dynamics on Gustatory Cortex Function

Keywords: Taste processing, conditioned taste aversion, taste neophobia

MICHAEL LEE CIARDULLO SEED GRANT

Aakanksha Singhvi, Ph.D.
Fred Hutchinson Cancer Center
Basic Sciences Division

Project Title: Roles of Glia in Neural Aging

Keywords: Aging, neurodegeneration, nervous system function

Andre M. M. Sousa, Ph.D.
University of Wisconsin-Madison
Department of Neuroscience

Project Title: Cerebellin 2 Dysregulation Mediates Synaptic Deficiency in Down Syndrome

Keywords: Down syndrome, neurodevelopment, synaptic function

Dmitry Velmeshev, Ph.D.
Duke University
Department of Neurobiology

Project Title: Understanding the Role of Epigenetic Regulation During Human Neural Lineage Commitment

Keywords: Autism, brain development, neurodevelopmental and psychiatric disorders

Brain Research Foundation
Innovate. Explore. Discover.

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Join us on **November 8, 2023**, at **The Four Seasons Chicago** as we celebrate our **70th Anniversary!**

Founded in Chicago in 1953, we are excited to celebrate with all our friends, scientists, and donors who have made funding 70 years of hope, new treatments, and advances in neuroscience a reality.

For more information, to make reservations or for sponsorship opportunities, please email sjaggi@theBRF.org